

1. (New) A replication defective hepadnavirus particle, wherein a region of the pre-S and S-gene of the hepadnavirus genome have been deleted and replaced by a heterologous gene such that the sequences for RC and RII that are essential for producing reverse transcriptase are retained.
2. (New) The replication defective hepadnavirus particle of claim 1, wherein the heterologous gene encodes one of a cytokine or a chemokine.
3. (New) The replication defective hepadnavirus particle of claim 2, wherein the cytokine is selected from the group consisting of TNF $\alpha$ , IFN $\beta$ , IL-18, IFN- $\gamma$  and IL-12.
4. (New) A pharmaceutical composition comprising:
  - a replication defective hepadnavirus with a region of its pre-S-genes deleted and replaced with a heterologous gene such that the sequences of the RC r RII that are essential for producing reverse transcriptase are retained, and
  - a pharmaceutically acceptable carrier.
5. (New) The pharmaceutical composition comprising:
  - a replication defective hepadnavirus with a region of its pre-S-gene deleted and replaced with a heterologous gene that

the sequences of the RC or RII that are essential for producing reverse transcriptase are retained, and

- a helper virus

6. (New) A method of producing replication defective hepadnavirus particles at a titer suitable for infecting hepatocytes comprising:

- co-transfected hepatocyte cells of a hepatoma cell line with:
  - (i) replicating defective hepadnavirus constructs, wherein a region of one of a pre-S or an S-gene of the hepadnavirus DNA has been replaced with a gene encoding a heterologous gene while retaining one of an RC or RII signal, such that the expression of the gene encoding a cytokine is regulated by regulatory sequences of the [pre-S] S-gene; and
  - (ii) a helper construct for transcomplementing lacking viral gene products;
- culturing the hepatocytes until infectious viral particles are produced; and
- recovering the infectious particles.

7. (New) The method of claim 39, wherein the cell line is stably transfected with the helper construct and serves as a packaging cell line.

8. (New) The method of claim 7, wherein the replication defective hepadnavirus particles are human hepatitis B virus particles
9. (New) The method of claim 7, wherein the heterologous gene replaces sequences of the S-gene.
10. (New) The method of claim 7, wherein the heterologous gene replaces a region of the S-gene under control of the endogenous S-promoter.
11. (New) The method of claim 7, wherein the heterologous gene is inserted such that one of an authentic AUG codon of the S-gene or nucleotides encoding further amino acids of the S-protein are fused in frame to the 5'end of the heterologous gene.
12. (New) The method of claim 7, wherein the heterologous gene encodes a modulating agent.
13. (New) The method of claim 7, wherein the heterologous gene encoded for a cytokine.

14. (New) The method of claim 13, wherein the cytokine is selected from the group consisting of IFN $\alpha$ , IFN $\beta$ , IFN $\gamma$ ; TNF $\alpha$ , IL-12 and IL-18.
15. (New) A method for producing replication defective recombinant hepadnavirus particles capable of expressing a heterologous gene in hepatocytes comprising:
  - replacing an S-gene in a hepatitis B virus genome with the heterologous gene such that the expression of the heterologous gene is regulated by an S-promoter;
  - producing a replication deficient hepadnavirus by means of a helper plasmid transcomplementing viral gene products such that the lacking viral gene products are present;
  - infecting hepatocytes with the recombinant hepadnavirus, whereby the heterologous gene is delivered into the hepatocyte and expressed in the hepatocyte.
16. (New) A recombinant HBV genome, wherein an S-gene in the HBV genome is deleted and replaced by a heterologous gene and wherein the sequences for RC and RII that are essential for reverse transcription are retained.

17. (New) The recombinant HBV genome of claim 16, wherein the heterologous gene is under the control of the endogenous S promoter.
18. (New) The recombinant HBV genome of claim 16, wherein the heterologous gene encodes an immunomodulator.
19. (New) The recombinant HBV genome of claim 16, wherein the heterologous gene encodes one of a cytokine or a chemokine.
20. (New) The recombinant HBV genome of claim 17, wherein the immuno modulator is selected from the group consisting of IFN $\alpha$ , IFN $\beta$ , IFN $\gamma$ , TNF $\alpha$ , IL-18 or IL-12.